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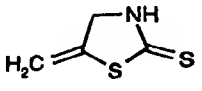
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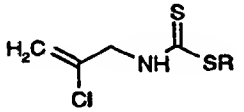
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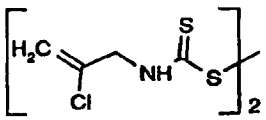
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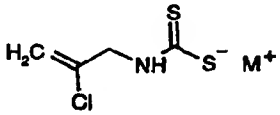
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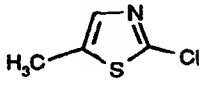
(VI)

(57) Abstract

The invention relates to a process for the preparation of 2-chloro-5-chloromethyl-thiazole, which is employed as intermediate in the preparation of compounds having a pesticidal action, which process comprises reacting a compound of formula (II), in free form or in salt form, (III), (IV), (V) or (VI) with a chlorinating agent, where R and M^+ are as defined in claim 1; to the compounds of the formulae (III) and (IV), which are used in this process as intermediates; and to the use of, and a process for the preparation of, the compounds of formulae (III) and (IV).

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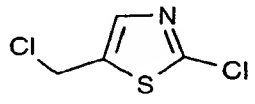
Process for the preparation of 2-chloro-5-chloromethyl-thiazole

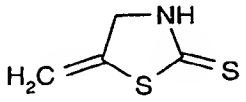
The invention relates to a process for preparing the known compound of the formula



I,

which comprises

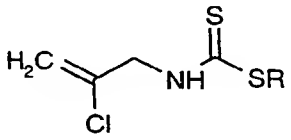
a) reacting the known compound of the formula



II,

in free form or in salt form, with a chlorinating agent, or

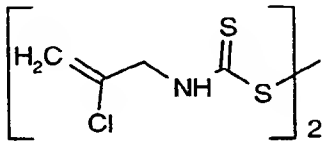
b) reacting a compound of the formula



III,

which is known or can be prepared by methods known per se and in which R is C_1-C_6alkyl, C_3-C_6cycloalkyl or an unsubstituted or mono- to pentasubstituted aryl or aryl-C_1-C_4alkyl group, where the substituents are selected from the group consisting of halogen and C_1-C_4alkyl, with a chlorinating agent, or

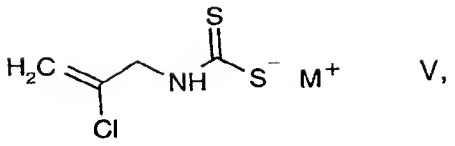
c) reacting the compound of the formula



IV

with a chlorinating agent, or

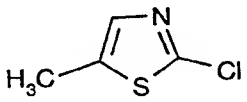
d) reacting a compound of the formula



V,

which is known or can be prepared by methods known per se and in which M^+ is an alkali metal ion, one equivalent of an alkaline earth metal ion or is a nonalkylated ammonium ion or an ammonium ion which is alkylated with from one to four identical or different alkyl radicals, and is preferably a potassium ion or, in particular, a sodium ion, with a chlorinating agent, or

e) reacting the compound of the formula



VI,

which is known, in the presence or absence of a free-radical catalyst, with a chlorinating agent, or

f1) first reacting the compound of the formula II or the compound 2-mercapto-5-methyl-thiazole, in each case in free form or in salt form, with a chlorinating agent, and

f2) subjecting the compound of the formula VI which is obtainable in this way to further reaction, with or without isolating it, with a chlorinating agent in accordance with variant e), or

g) subjecting a compound of the formula V either

g1.1) first to treatment with a base and

g1.2) the compound of the formula II thus obtainable, in free form or in salt form, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant a) or in accordance with variant f1/f2), or

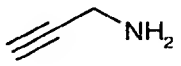
g2.1) first to reaction with a compound of the formula RX, which is known or can be prepared by methods known per se and in which R is as defined for the formula III and X is a leaving group, and

g2.2) the compound of the formula III thus obtainable, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant b), or

g3.1) first of all to reaction with an oxidizing agent, in the presence or absence of a base, and

g3.2) the compound of the formula IV thus obtainable, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant c), or

h1) reacting the compound of the formula



VII,

which is known, first of all with carbon disulfide, in the presence or absence of a base, and

h2) further reacting the compound of the formula II thus obtainable, in free form or in salt form, with or without isolating it, with a chlorinating agent in accordance with variant a) or in accordance with variant f1/f2);

to the compounds of the formulae III and IV, which are employed in this process as intermediates; and to the use of, and a process for the preparation of, the compounds of the formulae III and IV.

2-Chloro-5-chloromethylthiazole I is an important intermediate in the preparation of compounds having a pesticidal action, as are described, for example, in EP-A-0 192 060.

Unless defined otherwise, the general terms used above and below have the following meanings.

Halogen - both as a group on its own and as a structural element of other groups and compounds, such as of haloalkyl and halocyclopropyl - is fluorine, chlorine, bromine or iodine, especially fluorine, chlorine or bromine, in particular fluorine or chlorine, and most especially chlorine.

Compounds and groups containing carbon include, unless defined otherwise, in each case from 1 up to and including 6, preferably from 1 up to and including 3, and in particular 1 or 2, carbon atoms.

Cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, preferably cyclopropyl.

Alkyl - both as a group per se and as a structural element of other groups and compounds, such as of phenylalkyl and haloalkyl - is (always taking into account the particular number of

carbon atoms in the relevant group or compound) either straight-chain, i.e. methyl, ethyl, propyl, butyl, pentyl or hexyl, or branched, e.g. isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl or isohexyl.

Aryl is phenyl oder naphthyl, especially phenyl.

Depending on requirements, the reactions described above and below are carried out in the presence or absence of an appropriate solvent or diluent or mixture thereof, with cooling, at room temperature or heating, for example in a temperature range from about -80°C to the boiling temperature of the reaction medium, preferably from about -60°C to about +200°C, in a closed vessel under atmospheric, elevated or reduced pressure, under an inert gas atmosphere and/or under hydrogen-free conditions. Particularly advantageous reaction conditions are described below and can be inferred in particular from the Preparation Examples.

Variant a):

Examples of suitable chlorinating agents are elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride or mixtures of two or more of these compounds, preferably elemental chlorine, sulfuryl chloride or a mixture of these two compounds, particularly preferably sulfuryl chloride.

The reactants can be reacted with one another without adding a solvent or diluent. However, the addition of a solvent or diluent or mixture thereof may also be advantageous, its amount not being critical. Examples of such solvents or diluents are: water; alcohols, such as methanol, ethanol, propanol, isopropanol, butanol, ethylene glycol or glycerol, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, such as benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene or tetrachloroethene; ethers, such as diethyl ether, dipropyl ether, diisopropyl ether, dibutyl ether, tert-butyl methyl ether, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol dimethyl ether, dimethoxydiethyl ether, tetrahydrofuran or dioxane; amides, such as N,N-dimethylformamide, N,N-diethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone or hexamethylphosphoramide; nitriles, such as acetonitrile or propionitrile; and sulfoxides, such as dimethyl sulfoxide. If reaction is carried out in the

presence of an organic acid, then it is also possible for acids employed in excess, for example strong organic carboxylic acids, such as unsubstituted or substituted - for example by halogen - C_1-C_4alkanecarboxylic acids, examples being formic acid, acetic acid or propionic acid, to be used as solvent or diluent. The reaction is preferably carried out in the presence of a halogenated hydrocarbon, especially in dichloromethane.

Reaction takes place advantageously in a temperature range from about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant a) a compound II is reacted at from 0 to 40°, preferably from 10 to 15°, with a chlorinating agent, preferably sulfuryl chloride.

Reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 0.5 to 4 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

The yields obtained are generally good. It is possible to attain a yield of about 70 % of the theoretical yield.

Preferred conditions for the reaction are described in Examples H1 to H3.

Variant b):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant b), a compound III is reacted at -10 to 40°, preferably 0°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H4.

Variant c):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant c), a compound IV is reacted at -10 to 40°, preferably 0°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H5.

Variant d):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent

or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Variant e):

Examples of suitable free-radical catalysts are azobis(isobutyronitrile) or, in particular, dibenzoyl peroxide.

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant e), a compound VI is reacted at 10 to 120°, preferably 80°, with a chlorinating agent, preferably N-chlorosuccinimide.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 100 hours is preferred, especially from 12 to 72 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H6.

Variant f1/f2):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +80°C, preferably from about -10°C to about +40°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant f1/f2), a compound II is initially reacted at -10 to 40°, preferably 0°, with a chlorinating agent, preferably sulfuryl chloride, to give a compound of the formula VI which then, preferably after it has been isolated, is subjected to further reaction with a further chlorinating agent, preferably N-chlorosuccinimide.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 100 hours is preferred, especially from 1 to 72 hours, preferably from 12 to 72 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

2-Mercapto-5-methyl-thiazole, which can be used also in its tautomeric form (2-thioxo compound), can be obtained, for example, by acid treatment of the compound of the formula II.

Preferred conditions for the reactions are described in Examples H6, H7 and H9.

Variant g1.1):

Examples of suitable bases for facilitating the reaction are alkali metal or alkaline earth metal hydroxides, hydrides, amides, alkanolates, acetates, carbonates, dialkylamides or alkylsilylamides, alkylamines, alkylenediamines, nonalkylated or N-alkylated, saturated or unsaturated cycloalkylamines, basic heterocycles, ammonium hydroxides and carbocyclic amines. Specific examples are sodium hydroxide, hydride, amide, methanolate, acetate and carbonate, potassium tert-butanolate, hydroxide, carbonate and hydride, lithium

diisopropylamide, potassium bis(trimethylsilyl)amide, calcium hydride, triethylamine, diisopropylethylamine, triethylenediamine, cyclohexylamine, N-cyclohexyl-N,N-dimethylamine, N,N-diethylaniline, pyridine, 4-(N,N-dimethylamino)pyridine, quinuclidine, N-methylmorpholine, benzyltrimethylammonium hydroxide and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU).

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +80°C, preferably from about -10°C to about +40°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 100 hours is preferred, especially from 12 to 72 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Variant g1.2):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant g1.2), a compound II is reacted at 0 to 40°, preferably 10 to 15°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 0.5 to 4 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Examples H1 to H3, H6, H7 and H9.

Variant g2.1):

Suitable leaving groups X are, for example, hydroxyl, C_1-C_8alkoxy, halo-C_1-C_8alkoxy, C_1-C_8alkanoyloxy, mercapto, C_1-C_8alkylthio, halo-C_1-C_8alkylthio, C_1-C_8alkanesulfonyloxy, halo-C_1-C_8alkanesulfonyloxy, benzenesulfonyloxy, toluenesulfonyloxy and halogen, preferably toluenesulfonyloxy, trifluoromethanesulfonyloxy and halogn, especially halogen.

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 0.5 to 4 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Variant g2.2):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant g2.2), a compound III is reacted at -10 to 40°, preferably 0°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H4.

Variant g3.1):

Examples of suitable oxidizing agents are air, nitrogen monoxide, elemental halogens, alkali metal chlorates, inorganic peroxides, for example hydrogen peroxide, or sodium perborate, organic peroxides, for example benzoyl peroxide, or dimethyl sulfoxide, preferably elemental halogens or hydrogen peroxide, especially iodine.

Suitable bases for facilitating the reaction are, for example, of the type indicated under variant g1.1).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant g3.1), a compound V is reacted at -10 to 40°, preferably 0°, with an oxidizing agent, preferably iodine.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 0.5 to 4 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H8.

Variant g3.2):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant g3.2), a compound IV is reacted at -10 to 40°, preferably 0°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H5.

Variant h1):

Examples of suitable bases for facilitating the reaction are those indicated under variant g1.1).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Variante h2):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant h2), a compound II is reacted at 0 to 40°, preferably 10 to 15°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 0.5 to 4 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Examples H1 to H3, H6, H7 and H9.

The invention likewise provides starting materials and intermediates which are novel and which are used in accordance with the invention to prepare compound I, a process for their preparation, and their use as starting materials and intermediates for preparing the compound I; this pertains in particular to the compounds III and IV.

The invention likewise provides a process for the preparation of the compounds III and IV. The compound III can be prepared, for example, as described under variant g2.1). The compound IV can be prepared, for example, as described under variant g3.1).

The invention likewise provides for the use of the compound III or IV as an intermediate in the novel process for the preparation of the compound I.

The invention additionally provides starting materials and intermediates, in each case in free form or in salt form if applicable, which are novel and which are used in accordance with the invention for preparing compounds II, III, IV and VI and/or their salts, and to a process for their preparation, and for their use as starting materials and intermediates for preparing compounds II, III, IV and VI.

The compounds II, V, VI and VII are known or, where novel, can be prepared in analogy to known compounds.

The invention relates to all those process embodiments in which the starting material is a compound obtainable as an initial product or intermediate at any stage of the process and in which all or some of the missing steps are carried out or in which a starting material is used in the form of a derivative or salt and/or its racemates or enantiomers or, in particular, is formed under the reaction conditions.

The invention relates in particular to the processes described in Examples H1 to H9.

The examples which follow serve to illustrate the invention. They do not restrict the invention. Temperatures are given in degrees Celsius.

Examples

Example H1: 2-Chloro-5-chloromethylthiazole from 5-methylenethiazolidine-2-thione (compound II)

4 g of chlorine gas are passed at 10-15°C into a solution of 100 ml of acetic acid and 7 ml of water. Subsequently, at the same temperature, 9.2 g of 5-methylenethiazolidine-2-thione, 12 ml of 30 % sodium hydroxide solution, 28 ml of water and 21 g of chlorine gas are metered in over the course of 2-3 hours. Then 100 ml of water are added to this reaction mixture, and extraction is carried out three times with 30 ml of toluene. The organic phase is dried over sodium sulfate and concentrated in vacuo at 45°C to give the title compound in a yield of 56 % (melting point: 35°C).

Example H2: 2-Chloro-5-chloromethylthiazole from 5-methylenethiazolidine-2-thione (compound II)

1.31 g of 5-methylenethiazolidine-2-thione are added in portions at 0°C, with stirring, to a solution of 5.4 g of sulfuryl chloride in 8 ml of dichloromethane and 0.72 ml of water. The reaction mixture is subsequently stirred at room temperature for 1 hour. The mixture is then adjusted to a pH of 2 with 30 % sodium hydroxide solution, and the organic phase is separated off, dried over sodium sulfate and concentrated in vacuo to give the title compound in a yield of 70 % (melting point: 35°C).

Example H3: 2-Chloro-5-chloromethylthiazole from 5-methylenethiazolidine-2-thione (compound II)

1 ml of water at -5°C and then, at the same temperature over the course of 5 minutes, 1.4 g of 5-methylenethiazolidine-2-thione in five portions are added to a mixture of 13 ml of dichloromethane and 10 g of sulfuryl chloride. The reaction mixture is then diluted with 20 ml of water and 33 ml of dichloromethane, it is neutralized with about 24 ml of 30 % sodium hydroxide solution, and the organic phase is separated off. The aqueous phase is subjected to extraction with 27 ml of dichloromethane, and the combined extracts are dried over sodium sulfate and concentrated in vacuo at 35°C, to give the title compound in a yield of 31 % (melting point: 35°C).

Example H4: 2-Chloro-5-chloromethylthiazole from benzyl 2-chloro-2-propenyldithio-carbamate (compound III, R=benzyl)

358 mg of sulfuryl chloride are slowly added dropwise with stirring at 0°C to a solution of 341 mg of benzyl 2-chloro-2-propenyldithiocarbamate in 0.3 ml of dichloromethane. After 18 hours the reaction mixture is concentrated in vacuo at room temperature, the residue is subjected to extraction with hexane, and the organic phase is dried over sodium sulfate and concentrated in vacuo to give the title compound (melting point: 35°C).

Example H5: 2-Chloro-5-chloromethylthiazole from compound IV

283 mg of sulfuryl chloride are slowly added dropwise with stirring at 0°C to a solution of 135 mg of the compound IV in 0.2 ml of dichloromethane. The reaction mixture is stirred at room temperature for 18 hours and subjected to extraction with hexane, and the organic phase is dried over sodium sulfate and concentrated in vacuo to give the title compound (melting point: 35°C).

Example H6: 2-Chloro-5-chloromethylthiazole from 2-chloro-5-methylthiazole (compound VI)

5 mg of dibenzoyl peroxide in portions and then 155 mg of N-chlorosuccinimide are added at room temperature and with stirring to a solution of 124 mg of 2-chloro-5-methylthiazole in 4 ml of carbon tetrachloride. The reaction mixture is boiled under reflux for 64 hours, then a further 5 mg of dibenzoyl peroxide and 155 mg of N-chlorosuccinimide are added, and boiling is resumed for 8 hours. After cooling to room temperature, the suspension is filtered and the residue is washed with carbon tetrachloride. The organic phase is then concentrated in vacuo and the residue is purified by chromatography on silica gel with ethyl acetate/hexane (1:9), to give the title compound (melting point: 35°C).

Example H7: 2-Chloro-5-methylthiazole (compound VI) from 5-methylenethiazolidine-2-thione (compound II)

1.31 g of 5-methylenethiazolidine-2-thione are added in portions with stirring and at 0°C to a solution of 5.4 g of sulfuryl chloride in 8 ml of dichloromethane and 0.72 ml of water. The reaction mixture is subsequently stirred at room temperature for 1 hour and then adjusted to a pH of 2 using 30 % sodium hydroxide solution, and the organic phase is separated off, washed a number of times with water, dried over sodium sulfate and concentrated by evaporation, to give 2-chloro-5-methylthiazole with a boiling point of 174°C.

Example H8: Compound IV from sodium N-(2-chloro-2-propenyl)dithiocarbamate (compound V, M = sodium)

3.81 g of carbon disulfide are added with stirring and at 0°C to a solution of 4.58 g of 2-chloroallylamine in 25 ml of 2 N sodium hydroxide solution. A solution of 6.35 g of iodine and 4.32 g of potassium iodide in a little water is added to the solution of sodium N-(2-chloro-2-propenyl)dithiocarbamate obtainable as described in the first sentence of this example. The crude, oily product is separated off and is purified by chromatography on silica gel using ethyl acetate/hexane (1:10 to 1:1), to give the compound IV.

Example H9: 2-Chloro-5-methyl-thiazole (compound VI) from 2-mercapto-5-methyl-thiazole

1.35 g of 2-mercapto-5-methyl-thiazole are added in portions, with stirring and at 0°, to a solution of 5.8 g of sulfuryl chloride in 9 ml of dichloromethane and 720 mg of water. The reaction mixture is subsequently stirred at room temperature for 1 hour and then adjusted to a pH of 2 using aqueous sodium hydroxide solution (30%). The organic phase is separated

INTERNATIONAL SEARCH REPORT

Inter...onal Application No
PCT/EP 96/05564

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/32 C07C333/20 C07C333/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 446 913 A (TAKEDA CHEMICAL INDUSTRIES LTD.) 18 September 1991 see whole document -----	1-68

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 1997	14. 04. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Helps, I

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/05564

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 446913 A	18-09-91	CA 2038203 A	17-09-91
		IL 97565 A	29-06-95
		JP 4234864 A	24-08-92
		US 5180833 A	19-01-93

RECD 16 MAR 1998
WIPO PCT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
PI/5-20691/A		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP96/05564	12/12/1996	21/12/1995
International Patent Classification (IPC) or national classification and IPC		
C07D277/32		
Applicant		
NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☒	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/06/1997	12. 03. 98
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Helps, I Telephone No. (+49-89) 2399-8209

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP96/05564

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

   Description, pages:

   1-17 as originally filed

   Claims, No.:

   1-68 as originally filed

2. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-68
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2-25,48-58,62,66-68
	No:	Claims	1,26-47,59-61,63-65
Industrial applicability (IA)	Yes:	Claims	1-68
	No:	Claims	

2. Citations and explanations

   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

IV. LACK OF UNITY OF INVENTION.

The document EP-A-0,446,913 describes the preparation of 2-chloro-5-chloromethyl thiazole from the reaction of an allyl isothiocyanate with a chlorinating agent. The use of a chlorinating agent cannot be seen as a novel feature- common to processes (a)-(e) in claim 1. The processes (a)-(e) of claim 1 contain different solutions to the problem of providing alternative processes for the preparation of 2-chloro-5-chloromethyl thiazole. The starting materials (III), (IV) and (V), used in processes (b) - (d) of claim 1, form a group of dithiocarbamic acid derivatives which are a different class of compound from the cyclic thiazole derivative (II) and (V) used as starting material in process (a) and (e). The chlorination of 5-methylidne-thiazolidin-2-thione in process (a) of claim 1, appears to proceed via the formation of 2-chloro-5-methyl thiazole (VI) with subsequent allylic chlorination as in process (e). This appears to be a different type of reaction to the processes (b)-(d), which use a different class of starting material. Consequently, the present application is considered to contain two inventions, each drawn to a different solution to the problem of providing an alternative process of preparation of 2-chloro-5-chloromethyl thiazole, namely;

1). Process of preparation of 2-chloro-5-chloromethyl thiazole starting from 5-methylene thiazolidin-2-one or 2-chloro-5-methyl thiazole. (claims 1, 2-14, 48-59, 62)

2) Process of preparation of 2-chloro-5-chloromethyl thiazole starting from a dithiocarbamic derivative of formula (III), (IV) or (V) (claims 1, 15-47, 60,61, 63-68).

V. CITATIONS AND EXPLANATIONS.

The following documents are cited in this report.

EP-A-0,446,913 (A)
Houben-Weyl "Methoden der Organischen Chemie",
Band IX, p.869-73 (B)

The novel feature of the process of claim 1 is the choice of the compounds (I)-(VI) as starting materials in the processes (a)-(e), or as intermediates in the processes (f)-(h) as described in the claim. The dependent claims 1-62 describing preferred

embodiments of the processes of claim 1 are novel by consequence.

The novel feature of the 2-chloro-2-propenyldithiocarbamate derivative of claim 63 is its dimeric form. Claim 64 drawn to a process for its preparation and claim 65 drawn to its use in the preparation of 2-chloro-5-chloromethyl thiazole are novel by consequence.

The novel feature of the 2-chloro-2-propenyl dithiocarbamate derivative of claim 66 is the group R, which is an alkyl, cycloalkyl or aryl group as defined in claim 1. Claim 67 drawn to a process for preparing compounds of claim 66 and claim 68 drawn to the use of the compounds of claim 66 for the preparation of 2-chloro-5-chloromethyl thiazole are novel by consequence.

Claims 1-68 therefore meet the Novelty requirements of Article 33(2) PCT.

Document (A), which represents the closest prior art, describes the preparation of 2-chloro-5-chloromethyl thiazole from 2-chloroallyl isothiocyanate with a chlorinating agent selected from sulfuryl chloride and chlorine gas (see examples 1-5). The process of the present application differs from that described in (A) in that the starting material is selected from N-2-chloroallyl dithiocarbamic acid ester, dimer or salt (formulae (III), (IV) or (V), or from the cyclic N-allyl dithiocarbamic ester of formula (II), or from 2-chloro-5-methyl thiazole of formula (VI).

It is known from Document (B) that dithiocarbamic acid salts are easily converted to isothiocyanates with a number of reagents, including phosgene which is a chlorinating agent (see page 871, paragraph ©). Also,document (B) teaches that isothiocyanates can be prepared from the reaction of salts of dithiocarbamic acids with iodine to give dithiocarbamic acid dimers, which react further with iodine to give isothiocyanates (see page 873, paragraph (e)). The skilled man would expect that the reaction of the N-chloroallyl dithiocarbamic acid salts of formula (V) would proceed via the formation of an isothiocyanate, which according to the teaching of document (A), reacts further with a chlorinating agent to give 2-chloro-5-chloromethyl thiazole. Since chlorine is also an oxidising agent, the skilled man would also expect the reaction of the dithiocarbamic acid esters of formula (IV) with chlorine to proceed via the formation of an isothiocyanate. Hence, it appears at first sight that the dithicarbamic acid salts of formula (V) and the dimers of formula (IV) are obvious alternative starting materials for

the preparation of 2-chloro-5-chloromethyl thiazole.

Consequently, inventive step (Article 33(3) PCT) is not recognised for the process of claim 1, and of the dependent claims 26-36, 27-47 and 59-61 drawn to the preparation of 2-chloro-5-chloromethyl thiazole from the dithiocarbamic acid salts and dimers (IV) and (V) because the problem of providing an alternative preparation of 2-chloro-5-chloromethyl thiazole appears to have been solved in an obvious manner by using the compounds (IV) or (V) as starting materials or intermediates. The compound of claim 63 as well as claims 64-65 drawn to its preparation and use cannot be considered inventive since the compound of claim 63 does not contribute to an inventive process.

Starting form Document (A) it was not obvious to the skilled man to use the starting materials (II)-(III) and (VI) for the preparation of 2-chloro-5-chloromethyl thiazole. Inventive step (Article 33(3) PCT) can be recognised for claims 2-25, 48-58 and 62 because the problem of providing an alternative process for the preparation of 2-chloro-5-chloromethyl thiazole has been solved in a non obvious manner by the choice of compounds (II), (III) or (VI) as starting materials or intermediates.

VII. CERTAIN DEFECTS IN THE INTERNATIONAL APPLICATION.

The requirements of Rule 5.1(a)(ii) PCT have not been met because Documents (A) and (B) have not been mentioned in the description and the relevant prior art disclosed therein has not been briefly discussed.

09/091333

#5

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

U.S. APPLICATION NO.		FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/091,333		OSULLIVAN A	PI520691APCT

INTERNATIONAL APPLICATION NO.
PCT/EP96/05564

5611

MICHAEL W GLYNN
NOVARTIS CORPORATION
564 MORRIS AVENUE
PATENT & TRADEMARK DEPARTMENT
SUMMIT NJ 07901-1027

I.A. FILING DATE	PRIORITY DATE
12/12/96	12/21/95

DATE MAILED: 12/08/98

NOTIFICATION OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

1. The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as ☐ a Designated Office (37 CFR 1.494), ☒ an Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is **ACCEPTED** for national patentability examination in the United States Patent and Trademark Office.

2. The United States Application Number assigned to the application is shown above and the relevant dates are:

26 OCT 1998
35 U.S.C. 102(e) DATE

26 OCT 1998
DATE OF RECEIPT OF 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371(C) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

3. ☐ A request for immediate examination under 35 U.S.C. 371(f) was received on _____ and the application will be examined in turn.

4. The following items have been received:
- ☒ U.S. Basic National Fee.
- ☒ Copy of the international application in:
  - ☐ a non-English language.
  - ☒ English.
- ☐ Translation of the international application into English.
- ☒ Oath or Declaration of inventors(s) for DO/EO/US.
- ☐ Copy of Article 19 amendments. ☐ Translation of Article 19 amendments into English.
  The Article 19 amendments ☐ have ☐ have not been entered.
- ☒ The International Preliminary Examination Report in English and its Annexes, if any.
- ☐ Copy of the Annexes to the International Preliminary Examination Report (IPER).
  - ☐ Translation of Annexes to the IPER into English.
  The Annexes ☐ have ☐ have not been entered.
- ☒ Preliminary amendment(s) filed 16 JUN 1998 and _____.
- ☐ Information Disclosure Statement(s) filed _____ and _____.
- ☐ Assignment document.
- ☐ Power of Attorney and/or Change of Address.
- ☐ Substitute specification filed _____.
- ☐ Statement Claiming Small Entity Status.
- ☒ Priority Document.
- ☒ Copy of the International Search Report ☒ and copies of the references cited therein.
- ☐ Other:

Applicant is reminded that any communication to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above. (37 CFR 1.5)

Vinita M. Wallace
Telephone: (703) 305-3436

FORM PCT/DO/EO/903 (December 1997)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 17 July 1997 (17.07.97)	
International application No. PCT/EP96/05564	**Applicant's or agent's file reference** PI/5-20691/A
International filing date (day/month/year) 12 December 1996 (12.12.96)	**Priority date** (day/month/year) 21 December 1995 (21.12.95)
Applicant O'SULLIVAN, Anthony, Cornelius et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 June 1997 (27.06.97)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

B. Fitzgerald

Telephone No.: (41-22) 338.83.38

09/091333 5610 Copy for the Elected Office (EO/US) PCT/EP96/05564

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

NOVARTIS AG
Patent and Trademark Dept.
Klybeckstrasse 141
CH-4002 Basle
SUISSE

Date of mailing (day/month/year) 29 May 1998 (29.05.98)	
Applicant's or agent's file reference PI/5-20691/A	**IMPORTANT NOTIFICATION**
International application No. PCT/EP96/05564	**International filing date** (day/month/year) 12 December 1996 (12.12.96)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
O'SULLIVAN, Anthony, Cornelius Birsigstrasse 135 CH-4054 Basle Switzerland	GB	CH
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
O'SULLIVAN, Anthony, Cornelius Mattenstrasse 8 CH-4058 Basel Switzerland	GB	CH
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer R. Raissi Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

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09/091337

Copy for the Elected Office (EO/US) 5810 PCT/EP96/05564

PAT[illegible]T COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

NOVARTIS AG
Patent and Trademark Dept.,
Klybeckstrasse 141
CH-4002 Basle
SUISSE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 29 May 1998 (29.05.98)	
Applicant's or agent's file reference PI/5-20691/A	**IMPORTANT NOTIFICATION**
International application No. PCT/EP96/05564	**International filing date** (day/month/year) 12 December 1996 (12.12.96)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
SENN, Marcel Engerfeldstrasse 3 CH-4310 Rheinfelden Switzerland	CH	CH
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SENN, Marcel Rte Chatel-St-Denis 57 CH-1807 Blonay Switzerland	CH	CH
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer R. Raissi Telephone No.: (41-22) 338.83.38

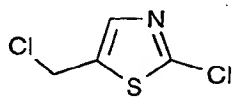
Form PCT/IB/306 (March 1994)

002059186

off, dried over sodium sulfate and concentrated by evaporation, to give 1.99 g of 2-chloro-5-methyl-thiazole with a boiling point of 174°.

WHAT IS CLAIMED IS:

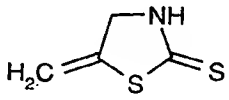
1. A process for preparing the compound of the formula



I,

which comprises

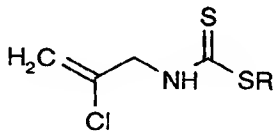
a) reacting the known compound of the formula



II,

in free form or in salt form, with a chlorinating agent, or

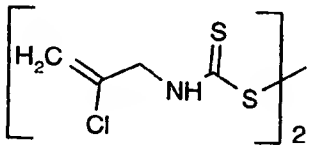
b) reacting a compound of the formula



III,

which is known or can be prepared by methods known per se and in which R is C_1-C_6alkyl, C_3-C_6cycloalkyl or an unsubstituted or mono- to pentasubstituted aryl or aryl-C_1-C_4alkyl group, where the substituents are selected from the group consisting of halogen and C_1-C_4alkyl, with a chlorinating agent, or

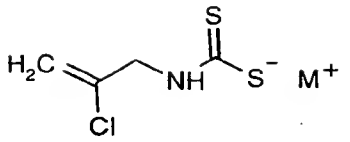
c) reacting the compound of the formula



IV

with a chlorinating agent, or

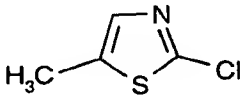
d) reacting a compound of the formula



V,

which is known or can be prepared by methods known per se and in which M^+ is an alkali metal ion, one equivalent of an alkaline earth metal ion or is a nonalkylated ammonium ion or an ammonium ion which is alkylated with from one to four identical or different alkyl radicals, and is preferably a potassium ion or, in particular, a sodium ion, with a chlorinating agent, or

e) reacting the compound of the formula



VI,

which is known, in the presence or absence of a free-radical catalyst, with a chlorinating agent, or

f1) first reacting the compound of the formula II or the compound 2-mercapto-5-methyl-thiazole, in each case in free form or in salt form, with a chlorinating agent, and

f2) subjecting the compound of the formula VI which is obtainable in this way to further reaction, with or without isolating it, with a chlorinating agent in accordance with variant e), or

g) subjecting a compound of the formula V either

g1.1) first to treatment with a base and

g1.2) the compound of the formula II thus obtainable, in free form or in salt form, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant a) or in accordance with variant f1/f2), or

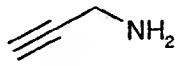
g2.1) first to reaction with a compound of the formula RX, which is known or can be prepared by methods known per se and in which R is as defined for the formula III and X is a leaving group, and

g2.2) the compound of the formula III thus obtainable, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant b), or

g3.1) first of all to reaction with an oxidizing agent, in the presence or absence of a base, and

g3.2) the compound of the formula IV thus obtainable, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant c), or

h1) reacting the compound of the formula

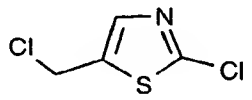


VII,

which is known, first of all with carbon disulfide, in the presence or absence of a base, and

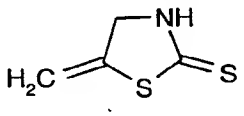
h2) further reacting the compound of the formula II thus obtainable, in free form or in salt form, with or without isolating it, with a chlorinating agent in accordance with variant a) or in accordance with variant f1/f2).

2. A process according to claim 1 for preparing the compound of the formula



I,

which comprises reacting the compound of the formula



II,

in free form or in salt form, with a chlorinating agent.

3. A process according to claim 2, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride and mixtures of two or more of these compounds.

4. A process according to claim 3, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, sulfuryl chloride and a mixture of these two compounds.

5. A process according to claim 4, wherein the chlorinating agent is sulfuryl chloride.

6. A process according to claim 2, wherein the solvent is selected from the group consisting of water, strong organic carboxylic acids, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, and mixtures of these solvents.

7. A process according to claim 6, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, propionic acid, benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene and tetrachloroethene, and mixtures of these solvents.

8. A process according to claim 7, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, dichloromethane, trichloromethane, tetrachloromethane and dichloroethane, and mixtures of these solvents.

9. A process according to claim 8, wherein the solvent is a mixture of water and dichloromethane.

10. A process according to claim 9, wherein the weight ratio of dichloromethane to water is from about 5 to about 50.

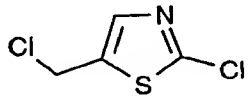
11. A process according to claim 10, wherein the weight ratio of dichloromethane to water is about 10 to about 30.

12. A process according to claim 2, wherein the reaction is carried out at from about -10°C to about +40°C.

13. A process according to claim 2, wherein the reaction period is from about 0.1 to about 4 hours.

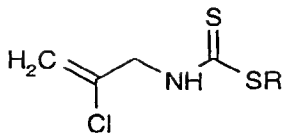
14. A process according to claim 13, wherein the reaction period is from about 0.5 to about 1.5 hours.

15. A process according to claim 1 for preparing the compound of the formula



I,

which comprises reacting a compound of the formula



III,

in which R is as defined in claim 1, with a chlorinating agent.

16. A process according to claim 15, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride and mixtures of two or more of these compounds.

17. A process according to claim 16, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, sulfuryl chloride and a mixture of these two compounds.

18. A process according to claim 17, wherein the chlorinating agent is sulfuryl chloride.

19. A process according to claim 15, wherein the solvent is selected from the group consisting of water, strong organic carboxylic acids, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, and mixtures of these solvents.

20. A process according to claim 19, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, propionic acid, benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene and tetrachloroethene, and mixtures of these solvents.

21. A process according to claim 20, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, dichloromethane, trichloromethane, tetrachloromethane and dichloroethane, and mixtures of these solvents.

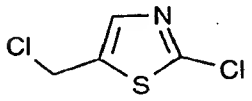
22. A process according to claim 21, wherein the solvent is dichloromethane.

23. A process according to claim 15, wherein the reaction is carried out at from about -10°C to about +40°C.

24. A process according to claim 15, wherein the reaction period is from about 1 to about 48 hours.

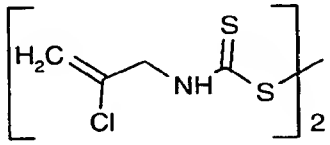
25. A process according to claim 24, wherein the reaction period is from about 12 to about 24 hours.

26. A process according to claim 1 for preparing the compound of the formula



I,

which comprises reacting a compound of the formula



IV

with a chlorinating agent.

27. A process according to claim 26, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride and mixtures of two or more of these compounds.

28. A process according to claim 27, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, sulfuryl chloride and a mixture of these two compounds.

29. A process according to claim 28, wherein the chlorinating agent is sulfuryl chloride.

30. A process according to claim 26, wherein the solvent is selected from the group consisting of water, strong organic carboxylic acids, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, and mixtures of these solvents.

31. A process according to claim 30, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, propionic acid, benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene and tetrachloroethene, and mixtures of these solvents.

32. A process according to claim 31, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, dichloromethane, trichloromethane, tetrachloromethane and dichloroethane, and mixtures of these solvents.

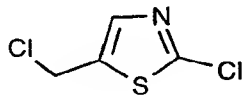
33. A process according to claim 32, wherein the solvent is dichloromethane.

34. A process according to claim 26, wherein the reaction is carried out at from about -10°C to about +40°C.

35. A process according to claim 26, wherein the reaction period is from about 1 to about 48 hours.

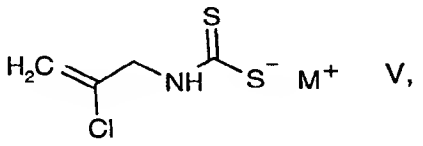
36. A process according to claim 35, wherein the reaction period is from about 12 to about 24 hours.

37. A process according to claim 1 for preparing the compound of the formula



I,

which comprises reacting a compound of the formula



V,

in which M^+ is as defined in claim 1, with a chlorinating agent.

38. A process according to claim 37, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride and mixtures of two or more of these compounds.

39. A process according to claim 38, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, sulfuryl chloride and a mixture of these two compounds.

40. A process according to claim 39, wherein the chlorinating agent is sulfuryl chloride.

41. A process according to claim 37, wherein the solvent is selected from the group consisting of water, strong organic carboxylic acids, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, and mixtures of these solvents.

42. A process according to claim 41, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, propionic acid, benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether,

hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene and tetrachloroethene, and mixtures of these solvents.

43. A process according to claim 42, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, dichloromethane, trichloromethane, tetrachloromethane and dichloroethane, and mixtures of these solvents.

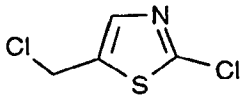
44. A process according to claim 43, wherein the solvent is dichloromethane.

45. A process according to claim 37, wherein the reaction is carried out at from about -10°C to about +40°C.

46. A process according to claim 37, wherein the reaction period is from about 1 to about 48 hours.

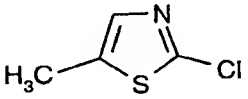
47. A process according to claim 46, wherein the reaction period is from about 12 to about 24 hours.

48. A process according to claim 1 for preparing the compound of the formula



I,

which comprises reacting the compound of the formula



VI,

with a chlorinating agent.

49. A process according to claim 48, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride and mixtures of two or more of these compounds.

50. A process according to claim 49, wherein the chlorinating agent is N-chlorosuccinimide.

51. A process according to claim 48, wherein the solvent is selected from the group consisting of water, strong organic carboxylic acids, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, and mixtures of these solvents.

52. A process according to claim 51, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, propionic acid, benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene and tetrachloroethene, and mixtures of these solvents.

53. A process according to claim 52, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, dichloromethane, trichloromethane, tetrachloromethane and dichloroethane, and mixtures of these solvents.

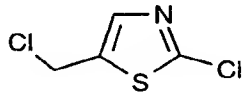
54. A process according to claim 53, wherein the solvent is tetrachloromethane.

55. A process according to claim 48, wherein the reaction is carried out at from about 20°C to about +80°C.

56. A process according to claim 48, wherein the reaction period is from about 1 to about 120 hours.

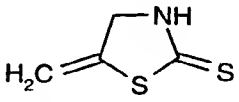
57. A process according to claim 56, wherein the reaction period is from about 48 to about 96 hours.

58. A process according to claim 1 for the preparation of the compound of the formula



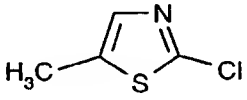
I,

which comprises first reacting the compound of the formula



II

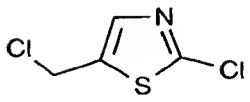
or the compound 2-mercapto-5-methyl-thiazole, in each case in free form or in salt form, with a chlorinating agent and further reacting the compound thus obtainable, of the formula



VI,

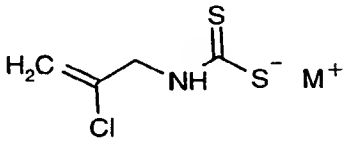
with or without isolating it, with a chlorinating agent.

59. A process according to claim 1 for the preparation of the compound of the formula



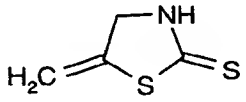
I,

which comprises treating a compound of the formula



V,

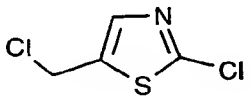
in which M^+ is as defined in claim 1, with a base and further reacting the compound thus obtainable, of the formula



II,

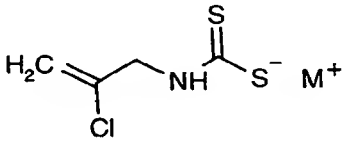
in free form or in salt form and with or without isolating it, with a chlorinating agent.

60. A process according to claim 1 for the preparation of the compound of the formula



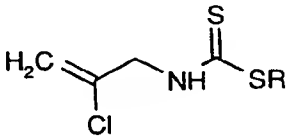
I,

which comprises reacting a compound of the formula



V,

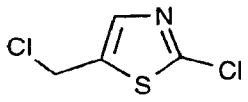
in which M^+ is as defined in claim 1, with a compound of the formula RX, in which R is as defined in claim 1 for the formula III and X is a leaving group, and further reacting the compound thus obtainable, of the formula



III,

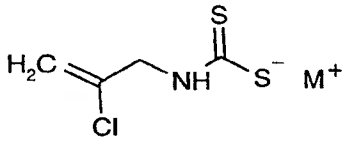
in which R is as defined in claim 1, with or without isolating it, with a chlorinating agent.

61. A process according to claim 1 for the preparation of the compound of the formula



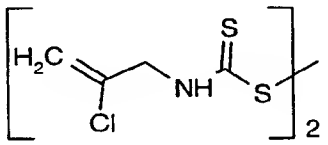
I,

which comprises reacting a compound of the formula



V,

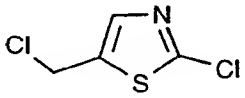
in which M^+ is as defined in claim 1, with an oxidizing agent, in the presence or absence of a base, and further reacting the compound thus obtainable, of the formula



IV,

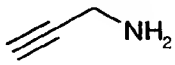
with or without isolating it, with a chlorinating agent.

62. A process according to claim 1 for the preparation of a compound of the formula



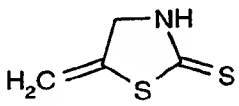
I,

which comprises reacting the compound of the formula



VII

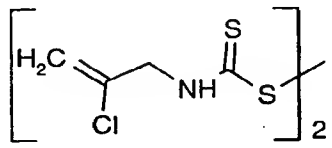
with carbon disulfide, in the presence or absence of a base, and further reacting the compound thus obtainable, of the formula



II,

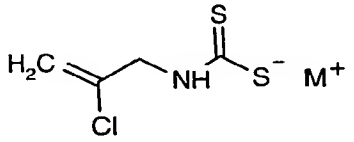
in free form or in salt form and with or without isolating it, with a chlorinating agent.

63. The compound of the formula



IV.

64. A process for the preparation of the compound according to claim 63, of the formula IV, which comprises reacting a compound of the formula

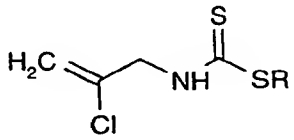


V,

in which M^+ is as defined in claim 1, with an oxidizing agent, in the presence or absence of a base.

65. The use of the compound according to claim 63, of the formula IV, in a process according to any one of claims 1, 26 to 36 and 61.

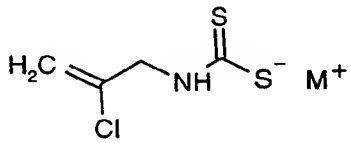
66. A compound of the formula



III,

in which R is as defined in claim 1.

67. A process for the preparation of a compound according to claim 66, of the formula III, which comprises reacting a compound of the formula



V,

in which M^+ is as defined in claim 1, with a compound of the formula RX, in which R is as defined in claim 1 for the formula III and X is a leaving group.

68. The use of a compound according to claim 66, of the formula III, in a process according to any one of claims 1, 15 to 25 and 60.

INTERNATIONAL SEARCH REPORT

Inter...onal Application No
PCT/EP 96/05564

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/32 C07C333/20 C07C333/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 446 913 A (TAKEDA CHEMICAL INDUSTRIES LTD.) 18 September 1991 see whole document -----	1-68

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
21 March 1997	14. 04. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Helps, I

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/05564

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 446913 A	18-09-91	CA 2038203 A	17-09-91
		IL 97565 A	29-06-95
		JP 4234864 A	24-08-92
		US 5180833 A	19-01-93

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PI/5-20691/A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 96/05564	12/12/1996	21/12/1995
Applicant		
NOVARTIS AG et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

Internati[illegible]pplication No
PCT/EP 96/05564

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/32 C07C333/20 C07C333/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 446 913 A (TAKEDA CHEMICAL INDUSTRIES LTD.) 18 September 1991 see whole document -----	1-68

☐ Further documents are listed in the continuation of box C.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 1997	14. 04. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Helps, I

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati[redacted]pplication No
PCT/EP 96/05564

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 446913 A	18-09-91	CA 2038203 A	17-09-91
		IL 97565 A	29-06-95
		JP 4234864 A	24-08-92
		US 5180833 A	19-01-93

(19) Europäisches Patentamt
European Patent Office
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(11) Publication number: **0 446 913 A1**

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(54) Process for the preparation of chlorothiazole derivatives.

(57) Novel processes for preparing 2-chlorothiazoles, useful as an intermediate for insecticides, from allyl isothiocyanate derivatives having the formula [II]:

$$CH_2 = \underset{\displaystyle X}{\overset{\displaystyle |}{C}} - CH_2NCS \qquad [\ II\ ]$$

wherein X represents a leaving group,
are simple and convenient reaction procedures under mild conditions without need of a large excess of a chlorinating agent. Further, processes for preparing 5-(aminomethyl)-2-chlorothiazole or salts thereof from the compound [II] achieve higher yields by simple, convenient and inexpensive procedures.

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inexpensive procedures.

SUMMARY OF THE INVENTION

Extensive studies were made by us on the process for preparing compound [I] and compound [III] or salts thereof in order to achieve the above-mentioned object. As a result of these studies, we have discovered that compound [I] of a high purity can be produced in a high yield through very simple reaction procedures and aftertreatments by reacting an allyl isothiocyanate derivative represented by the formula

$$CH_2 = \underset{\displaystyle X}{\overset{\displaystyle |}{C}} - CH_2NCS \qquad [II]$$

wherein X represents a leaving group with a chlorinating agent under mild conditions, unexpectedly without need of using a large excess of the chlorinating agent, that compound [III] or salts thereof can be produced by aminating the compound [I] thus prepared from compound [II] and that the compound [III] or salts thereof can be produced unexpectedly in a high yield by reacting the compound [I] with liquid ammonia or hexamethylenediamine. The present invention has been completed on the basis of these discoveries.

Thus the invention relates to (1) a process for preparing 2-chloro-5-(chloromethyl)thiazole (compound [I]) which comprises reacting compound [II] with a chlorinating agent, (2) a process for preparing 5-(aminomethyl)-2-chlorothiazole (compound [III]) or salts thereof which comprises reacting compound [II] with a chlorinating agent to give 2-chloro-5-(chloromethyl)thiazole (compound [I]) and then reacting the compound [I] thus obtained with an aminating agent, and (3) a process for preparing 5-(aminomethyl)-2-chlorothiazole (compound [III]) or salts thereof which comprises reacting compound [I] with liquid ammonia or hexamethylenetetramine.

These processes are excellently simple and advantageously useful on an industrial scale in the preparation of insecticides and other valuable compounds.

DETAILED DESCRIPTION OF THE INVENTION

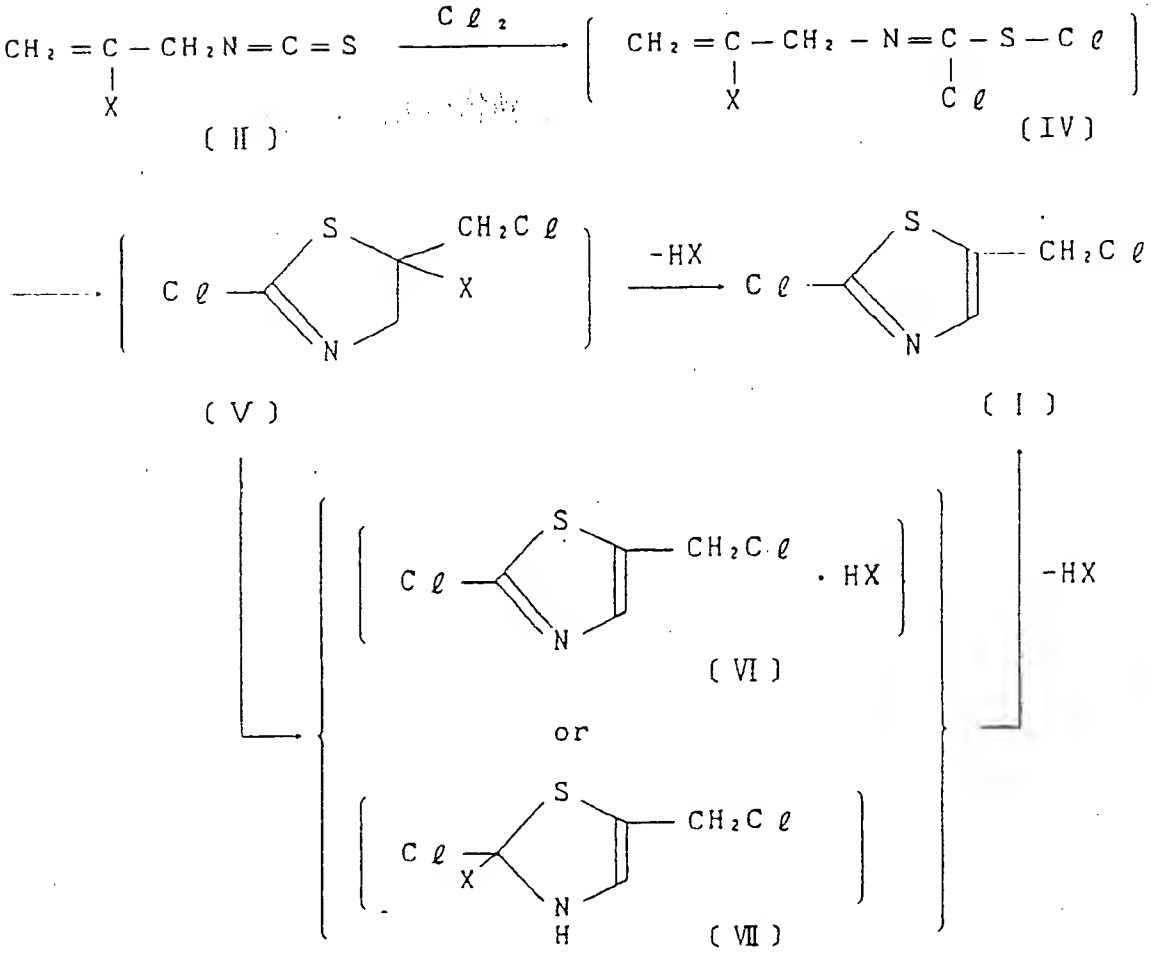
According to the invention, there are provided processes for preparing 2-chloro-5-(chloromethyl)thiazole (compound [I]) which comprises reacting the compound [II] with a chlorinating agent. The compound [I] which is excellently useful in synthesizing insecticides is selectively produced in an unexpected high yield.

The compound [I] thus produced can be converted into the compound [III] advantageously.

Another aspect of the invention provides processes for preparing 5-(aminomethyl)-2-chlorothiazole ([III]) or salts thereof which comprises reacting compound [II] with a chlorinating agent followed by the reaction of the compound [I] thus obtained with an aminating agent, or compound [I] with liquid ammonia or hexamethylenetetramine.

As the leaving group defined by X in the above formula is used, for example, halogen such as fluorine, chlorine, bromine or iodine; C_{1-4} alkylsulfonyloxy optionally substituted with 1 - 3 halogen atoms (such as Cl, Br or F) such as methanesulfonyloxy, ethanesulfonyloxy, butanesulfonyloxy or trifluoromethanesulfonyloxy; C_{6-10} arylsulfonyloxy optionally substituted with 1 - 4 lower alkyl groups (e.g. methyl or ethyl) or halogen atoms (e.g. Cl, Br or F) such as benzenesulfonyoxy, p-toluenesulfonyloxy, p-bromobenzenesulfonyloxy or mesitylenesulfonyloxy; C_{1-6} acyloxy optionally substituted with 1 - 3 halogen atoms (such as Cl,Br or F) such as acetyloxy, propionyloxy or trifluoroacetyloxy or C_{6-10} arylcarbonyloxy such as benzoyloxy. Usually, the compound [II] wherein X is chlorine (2-chloroallyl isothiocyanate) is most readily available.

The "chlorinating agent" represents chlorine and compounds releasing chlorine under reaction conditions such as sulfuryl chloride. The "aminating agent" represents ammonia (intended in the invention to include aqueous ammonia) and compounds in which ammonia is protected to prevent polyalkylation, for example, dicarboximides such as phthalimide and succinimide, sulfonamides such as p-toluenesulfonamide and trifluoromethanesulfonamide, carboxamides such as acetamide and trifluoroacetamide, carbamic acid esters such as tert-butyl carbamate and methyl carbamate, hexamethylenetetramine and trichloroamine. Additionally, if feasible, alkali metal salts of these compounds such as potassium amide, sodium amide, potassium phthalimide and sodium phthalimide are included. The protective group is removed by a known method except for the cases where ammonia or an alkali metal salt thereof is used as the aminating agent.

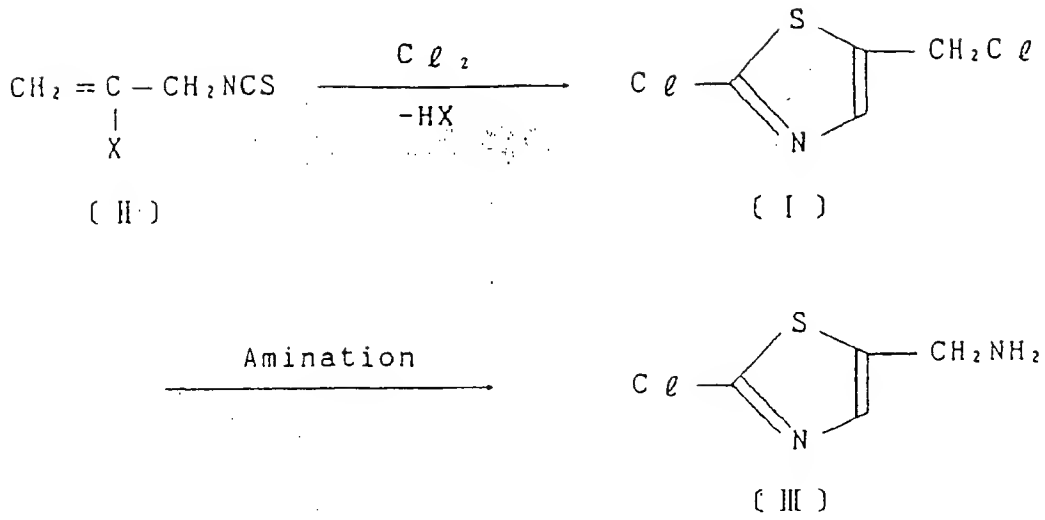


wherein X represents a leaving group as stated above.

Thus, chlorine is added to an allyl isothiocyanate derivative [II] to form a sulfenyl chloride derivative [IV] (called compound [IV] hereinbelow). Compound [IV] is then subjected to cyclization addition to give a 2-thiazoline derivative represented by the formula [V] (called compound [V]). Compound [V] in turn releases HX spontaneously or by heating or with a base to be converted to 2-chloro-5-(chloromethyl)-thiazole (compound [I]). In some cases, HX salt of compound [I] (called compound [VI]) or HX adduct of of compound [I] (called compound [VII]) is formed as an intermediate at this atage.

The reaction, if conducted at a low temperature or in diluted solution, tends to terminate upon formation of compound [IV] or compound [V], but if conducted at a high temperature and in the absence of solvent or in concentrated solution, tends to proceed until the desired 2-chloro-5-(chloromethyl)thiazole ([I]) is formed. Therefore, compound [I] may be prepared either by first carrying out the reaction at a low temperature or in diluted solution to produce compound [IV] or [V] as the main product and then raising the reaction temperature or concentrating, or doing both to produce compound [I], or by carrying out the reaction at a high temperature and in the absence of solvent or in concentrated solution from the beginning to produce compound [I]. The "low temperature", "high temperature", "diluted solution" and "concentrated solution" herein referred to are variable depending upon such factors as nature of the chlorinating agent, scale of the reaction and reaction time and cannot be specified. Usually, however, the "low temperature" represents a temperature between -20 - 20 °C, the "high temperature" a temperature between 30 - 100 °C, the "diluted solution" a solution in a concentration of about 20% or below, and the "concentrated solution" a solution in a concentration of about 40% or above.

In some cases, compound [I] is advantageously prepared by first producing the intermediate [V], [VI] or [VII] and then reacting it with a base. As the base are preferably used inorganic bases such as, for example, sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium



In the reaction, compound [I] is first prepared according to the conditions described for the method (A). The resulting compound [I] may be isolated and purified, or in some cases, it can be reacted with an aminating agent without isolation and purification. The aminating agent is preferably used in an amount of 0.8-1.5 equivalents on the basis of the compound [I] and may be used about 1.5 -50 equivalents in some cases.

This step is often carried out in an appropriate solvent, though it may be done in the absence of solvent. As the solvent is used, for example, water, an alcohol such as methanol, ethanol, n-propanol or isopropanol, an aromatic hydrocarbon such as benzene, toluene or xylene, a halogenated hydrocarbon such as dichloromethane or chloroform, a saturated hydrocarbon such as hexane, heptane or cyclohexane, an ether such as diethyl ether, tetrahydrofuran (called THF for short hereinbelow) or dioxane, a nitrile such as acetonitrile, a sulfoxide such as dimethylsulfoxide (called DMSO for short hereinbelow), a carboxamide such as N,N-dimethylformamide (called DMF for short hereinbelow), or an ester such as ethyl acetate. These solvents may be used either alone, or as required, in combination of two or more in an appropriate ratio, for example, a ratio of 1:1 - 1:10. If the reaction mixture is not in homogeneous phase, the reaction may also be carried out in the presence of a phase transfer catalyst, for example, a quaternary ammonium salt such as triethylbenzylammonium chloride, tri-n-octylmethylammonium chloride, trimethyldecylammonium chloride or tetramethylammonium bromide, or a crown ether.

This step may also be promoted by the addition of 0.1 - 10 equivalents, preferably 1.0 - 3 equivalents of a base. As the base may be used an inorganic base such as sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, calcium hydroxide, phenyllithium, butyllithium, sodium hydride, potassium hydride, sodium methoxide, sodium ethoxide, metallic sodium or metallic potassium, or an organic base such as triethylamine, tributylamine, N,N-dimethylaniline, pyridine, lutidine, collidine, 4-(dimethylamino)pyridine, or DBU. Said organic base itself may also be used as a solvent.

The reaction temperature and time in this step are usually -20°C - 150°C and 10 min.- 50 hours, preferably 0°C - 100°C and 1 hour - 20 hours, respectively.

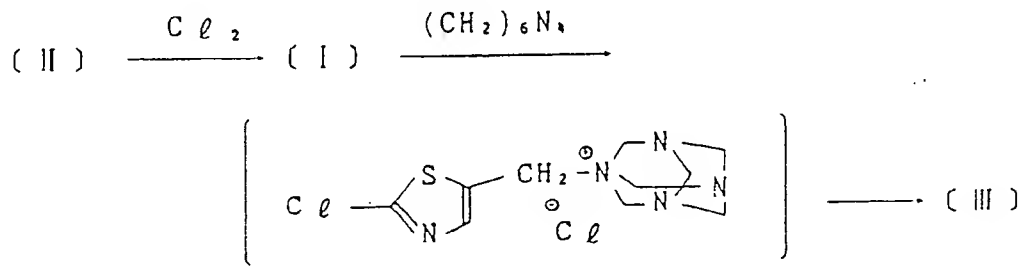
It is necessary to remove the protective group which is known per se except for the case where ammonia (including aqueous ammonia) or an an alkali metal salt thereof is used as the aminating agent. The removal can be effected in accordance with the procedures described, for example, in "Shin Jikken Kagaku Koza" (New Textbook Series of Chemical Experiments)(Maruzen), vol. 14-III, pp.1342 - 1349 and references cited therein.

More preferred reaction conditions with (i) aqueous ammonia, (ii) liquid ammonia, (iii) potassium or sodium phthalimide and (iv) hexamethylenetetramine as the aminating agent will be described below.

(i) With aqueous ammonia as the aminating agent

applicable. Thus, the intermediate [X] and 1.0 - 1.2 equivalents of hydrazine (or hydrazine hydrate) on the basis of the intermediate [X] can be reacted in an appropriate solvent (for example, alcohols and nitriles as mentioned above) at 0 °C - 100 °C for 1 hour - 10 hours to give compound [III] or a salt thereof.

(iv) With hexamethylenetetramine as the aminating agent

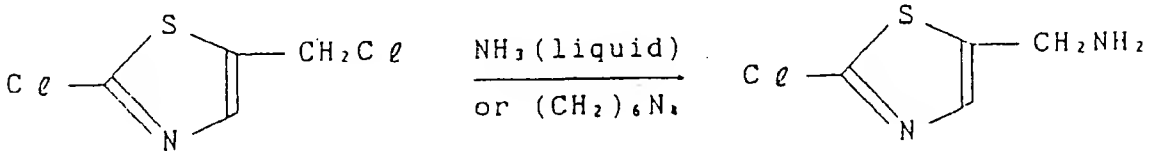


(II) → (I) → (III)

(XI)

First, compound [I] and hexamethylenetetramine are reacted to give a quaternary ammonium salt intermediate [XI]. Hexamethylenetetramine is used preferably in an amount of 1.0 - 1.5 equivalents on the basis of the compound [I]. The solvent is preferably an alcohol, a halogenated hydrocarbon or a nitrile as mentioned above though a variety of solvents may be employed. The reaction temperature and time are preferably 20 °C - 100 °C and 1 - 10 hours, respectively. The intermediate [XI] is preferably isolated at this stage but may be converted without isolation into compound [III]. Acid hydrolysis is usually employed for the hydrolysis of the intermediate [XI]. Thus, the intermediate [XI] is reacted preferably with 5 - 50 equivalents of an inorganic acid (such as hydrochloric, hydrobromic or sulfuric acid) on the basis of [XI]. The solvent is preferably water, an alcohol or a nitrile as mentioned above. When an organic solvent is used, it is preferably one containing about 5 - 50% of water. The reaction temperature and time are preferably 20 - 100 °C and 20 min. - 5 hours, respectively.

(C) 5-(Aminomethyl)-2-chlorothiazole [(II)] can be prepared by reacting 2-chloro-5-(chloromethyl)thiazole ([I]) with liquid ammonia or hexamethylenetetramine.



(I)

The reaction can proceed under the same reaction conditions as mentioned for the reaction of compound [I] obtained from compound [II] with an aminating agent in the latter part of the method (B). More preferably, the conditions under "(ii) with liquid ammonia as the aminating agent and (iii) with hexamethylenetetramine as the aminating agent" may be employed.

The compound [I] and compound [III] or salts thereof thus produced can be isolated by a known method such as concentration, concentration under reduced pressure, distillation, fractional distillation, solvent extraction, pH change, solvent change, chromatography, crystallization or recrystallization.

In the case where compound [III] is obtained in the above-mentioned process in free form, it can be converted by a conventional method into a salt, or vice versa.

As stated above, compound [I] and compound [III] or salts thereof are useful as a starting material for known insecticidal compounds. Moreover, it has been found that they are also useful as a starting material for novel insecticides. Thus, compound [I] prepared by the process according to the present invention is reacted with a compound represented by the formula

wherein each group has the same meaning as defined above or salts thereof.

It is preferable to use about 0.8 - 2.0 equivalents of compound [III] or a salt thereof on the basis of the compound [XIV] or a salt thereof. However, about 2.0 - 20 equivalents may be employed if the reaction is not hindered.

The reaction is carried out usually in a solvent as mentioned in the method (B) though it may also be done in the absence of solvent. A phase transfer catalyst may also be employed as stated in the method (B) if the reaction system is not in homogeneous phase.

The reaction may also be promoted by adding a base and/or a metallic salt in an amount of 0.01 - 10 equivalents, preferably 0.1 - 3 equivalents on the basis of the compound [XIV]. As the base may be used, for example, those which are referred to in the method (B). When an organic base is used it can also serve as a solvent. As the metal salt may be employed, for example, copper salts such as copper chloride, bromide, acetate and sulfate and mercury salts such as mercury chloride, nitrate and acetate.

Temperature and time of the reaction are usually -50 °C - 150 °C and 10 min. - 50 hours, preferably -30 °C - 100 °C and 30 min. - 20 hours, respectively.

As the lower alkyl group represented by R^1, R^2 and R^3 in the above formula is used, for example, methyl, ethyl, propyl or isopropyl, and as the lower carboxylic acyl, for example, formyl, acetyl or propionyl. As the cyclic amino group reperesented by R^1 and R^2 taken together with the adjacent nitrogen atom is used, for example, aziridino, azetidino, pyrrolidino, piperidino or morpholino.

As the lower alkoxy group represented by Y is used, for example, methoxy, ethoxy, propoxy or isopropoxy, and as the lower alkylthio, for example, methylthio, ethylthio, propylthio or isopropylthio.

As the salt of compounds [XII], [XIII], [XIV] and [XV] are used, for example, those which are mentioned above for compound [III].

As described above, use of the process according to the invention enables production of compounds [XIII] or salts thereof from compound [II] via compound [I], as well as of compounds [XV] or salts thereof from compound [II] via compound [I] and compound [III] or a salt thereof, or from compound [I] via compound [III] or a salt thereof.

Compounds [XIII] or salts thereof and compounds [XV] or salts thereof thus prepared possess a high insecticidal activity.

Examples

The invention will be described in more detail below with reference to Examples and Reference Examples. However, the invention is not intended to be limited to these examples.

Elution of the column chromatography in the examples and the reference examples were made under observation with TLC (thin layer chromatography). There were employed in the TLC observation Kieselgel $60F_{254}$ (70 - 230 mesh, Merck) as the TLC plate, a solvent used as the eluent in the chromatography as the developing solvent and a UV detector as the detecting method. As the silica gel for column chromatography was used Kieselgel 60 (70 - 230 mesh, Merck). The NMR represents a proton NMR using tetramethylsilane as the internal standard, being measured on VARIAN EM390 (90 MHz) and being indicated in terms of all δ value in ppm. The figures in ( ) for a mixed solvent used as the developing solvent indicate volume ratio of the solvents in the mixture.

Abbreviations in the examples and the reference examples have the following meanings.

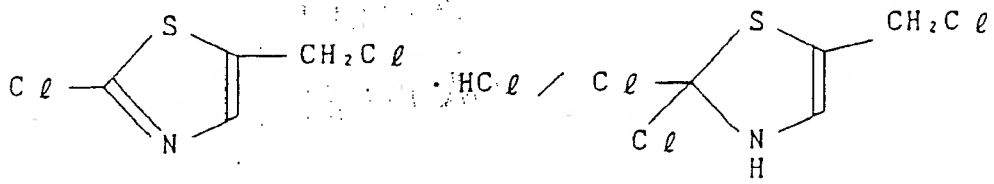
Me: methyl, Et: ethyl, s: singlet, br: broad, d: doublet, t: triplet, q: quartet, m: multiplet, dd:doublet of doublet, J: coupling constant, Hz: herz, $CDCl_3$: deutero-chloroform, DMSO-d_6: deutero-DMSO, %: % by weight, mp: melting point, bp: boiling point and room temperature means a temperature of ca. 15- 25 °C.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds and procedures. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention.

Example 1

Into a mixture of 13.4 g of 2-chloroallyl isothiocyanate and 10 mℓ of chloroform was introduced gaseous chlorine under cooling with ice (inner temperature of 10 °C or below) over one hour and 40 min. Weight of the gaseous chlorine absorbed was 7.71 g. At this stage, the products, according to NMR, were estimated as 2-aza-1,4-dichloro-1,4-pentadienesulfenyl chloride

temperature of 20°C or below. The main product at this stage was estimated as 2,5-dichloro-5-(chloromethyl)-2-thiazoline, and further concentration at 40 °C - 60°C converted the main product to the substance which was estimated as 2-chloro-5-(chloromethyl)thiazole hydrochloride or 2,2-dichloro-5-(chloromethyl)-4-thiazoline.



(NMR($CDCl_3$) : 4.79(2H, s), 7.70(1H, s))

Addition of chloroform to this product followed by addition of diluted aqueous ammonia or aqueous sodium bicarbonate and stirring at 20°C or below yielded 2-chloro-5-(chloromethyl)thiazole.

Example 6

A mixture of 1.0 g of 2-chloro-5-(chloromethyl)thiazole obtained by the procedures in Example 2, 4 mℓ of 25% aqueous ammonia and 6 mℓ of acetonitrile was placed in a stainless steel autoclave and reacted at 80°C for 2 hours.

After cooling, 0.6 mℓ of a 10N aqueous solution of sodium hydroxide and 12 mℓ of ethanol were added, and the mixture stirred at room temperature for 30min. The reaction mixture was concentrated followed by addition of 20 mℓ of dichloromethane and dried over anhydrous magnesium sulfate. Insoluble materials were separated by filtration and the filtrate was then concentrated. The concentrate was purified by column chromatography (eluted with dichloromethane-methanol 10:1) to afford 0.49 g of 5-(aminomethyl)-2-chlorothiazole as yellow liquid. NMR ($CDCl_3$): 1.66(2H, s), 4.02(2H, s), 7.36 (1H, s).

Example 7

A mixture of 0.50 g of 2-chloro-5-(chloromethyl)thiazole, 4 mℓ of 25% aqueous ammonia and 6 mℓ of acetonitrile was heated under reflux for 30 min. followed by supplement of 8 mℓ of 25% aqueous ammonia. The mixture was heated under reflux for 30 additional min. After-treatment in the same way as in Example 6 yielded 0.22 g of 5-(aminomethyl)-2-chlorothiazole.

Example 8

To a mixture of 27.5g of hexamethylenetetramine and 150 mℓ of chloroform was dropwise added 30.0 g of 2-chloro-5-(chloromethyl)thiazole over 30 min. while heating under reflux. The mixture was heated under reflux with stirring for 3 hours and then allowed to stand overnight. Crystals thus formed were separated by filtration and washed with 100 mℓ of chloroform. Combined filtrate and washing were concentrated to 100 mℓ. Crystals formed after being allowed to stand for half a day were separated by filtration and washed with 20 mℓ of chloroform. Combined filtrate and washing were treated two more times in the same way as above. There was obtained a total of 55.0 g (yield, 99.7%) of a quaternary ammonium salt.

A mixture of 32.5 g of the quaternary ammonium salt, 104 g of 36% hydrochloric acid, 97.5 mℓ of water and 325 mℓ of ethanol was stirred at 70°C for one hour and then allowed to stand overnight. Solids then formed were separated by filtration, and the filtrate was concentrated to about a half of the original volume. Solids formed were again separated by filtration, and the filtrate was concentrated to dryness. To the residue was added 100 mℓ of acetone, and insoluble materials collected by filtration. To the filtrate was added 250 mℓ of water, and pH adjusted with 6N aqueous sodium hydroxide to 13. The mixture was extracted three times with dichloromethane, and the dichloromethane layers washed with saturated aqueous sodium chloride, dried over anhydrous potassium carbonate and concentrated. There was obtained 14.3 g of crude 5-(aminomethyl)-2-chlorothiazole, which was purified by distillation under reduced pressure to give 10.5g of pure products, bp: 85°C/10. 5 mmHg.

Example 9

separation of insoluble materials and concentration. The residue was stirred in an oil bath at 140° C for 1 hour and distilled under reduced pressure. There was obtained 339.5 g of 2-chloroallyl isothiocyanate, bp 73 - 76° C/18 mmHg.

Reference Example 2

To a mixture of 13.0 g of N,N-dimethyl-N'-nitroguanidine, 5.90 g of powdery sodium hydroxide and 200 mℓ of dry DMF was dropwise added a solution of 2-chloro-5-(chloromethyl)thiazole in 15 mℓ of DMF over 2 hours while cooling with ice. The bath was removed, and stirring continued at room temperature for 13 hours followed by removal of the DMF by distillation under reduced pressure. To the residue was added 200 mℓ of acetonitrile followed by separation of insoluble materials by filtration on celite. The filtrate was purified by column chromatography (eluted with dichloromethane-acetonitrile 2:1- 1:2). There was obtained 6.45 g of 1-(2-chloro-5-thiazolylmethyl)-3,3-dimethyl-2-nitroguanidine (reference compound No.1), mp 155 - 160° C. Crystallization from ethanol raised mp to 165.5 - 166.5° C. NMR (DMSO-d_6): 2.96(6H, s), 4.50(2H, d, J = 5.8Hz), 7.56(1H, s), 8.53(1H, br t, J = 5.8 Hz).

Similarly, the following compounds were obtained: 1-(2-chloro-5-thiazolylmethyl)-3-ethyl-3-methyl-2-nitroguanidine (reference compound No.2, mp 165 - 167° C), 1-(2-chloro-5-thiazolylmethyl)-3,3-diethyl-2-niroguanidine (reference compound No. 3, syrup, NMR ($CDCl_3$): 1.23(6H, t, J = 7 Hz), 3.46(4H, q, J = 7.2 Hz), 4.60(2H, br s), 7.44(1H, s), 8.30(1H, br s)), 1- [1-(2-chloro-5-thiazolylmethyl)-2-nitroamidino] pyrrolidine (reference compound No.4, mp 185 - 188° C).

Reference Example 3

To a mixture of 5.0 g of S-methyl-N-nitroisothiourea and 25 mℓ of pyridine was dropwise added 11.3 g of acetic anhydride at room temperature over 10 min. After completion of the addition the mixture was stirred at room temperature for 5 hours, and the reaction mixture concentrated. The residue was poured onto 50 mℓ of 2N hydrochloric acid, and crystals then formed collected by filtration and dried. There was obtained 5.1 g of N-acetyl-S-methyl-N'-nitroisothiourea as white crystals, mp 109 - 110° C.

To a mixture of 0.22 g of N-acetyl-S-methyl-N'-nitroisothiourea and 5 mℓ of acetonitrile was dropwise added 0.2 g of 5-(aminomethyl)-2-chlorothiazole at -2° C. Stirring was continued at the same temperature for additional 1 hour, and then the reaction mixture concentrated. The residue solidified was recrystallized from ethanol to give 0.31 g of N-acetyl-N'-(2-chloro-5-thiazolylmethyl)-N''-nitroguanidine (reference compound No.5), mp 132 - 133° C. NMR ($CDCl_3$): 2.33(3H, s), 4.68(2H, d, J = 6 Hz), 7.50(1H, s), 9.60(1H, br), 11.85(1H, br).

Reference Example 4

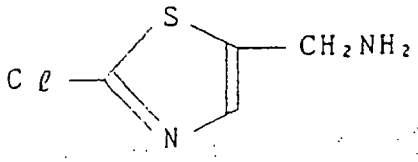
A mixture of 6.82 g of 5-(aminomethyl)-2-chlorothiazole, 7.26 g of 1,2-dimethyl-3-nitroisothiourea, 6.72g of anhydrous potassium carbonate, 4.81 g of cuprous chloride and 150 mℓ of acetonitrile was heated under reflux for 1 hour. Insoluble materials were separated by filtration while hot, and the filtrate concentrated. The concentrate was purified by column chromatography (eluted with dichloromethane-methanol 10:1). There was obtained 7.33 g of 1-(2-chloro-5-thiazolylmethyl)-3-methyl-2-nitroguanidine (reference compound No.6), mp 172 - 174° C (recrystallized from acetonitrile). NMR(DMSO-d_6):2.83(3H, d, J = 5 Hz), 4.53(2H, d, J = 5 Hz), 7.61(1H, s), 8.12(1H, br s), 9.00(1H, br s).

Reference Example 5

To a mixture of 0.50 g of 1,2-dimethyl-3-nitroisothiourea and 10 mℓ of pyridine was dropwise added 1.03g of acetic anhydride at room temperature. The mixture was stirred at room temperature for 1 hour, and then poured onto 150 mℓ of 2N hydrochloric acid followed by extraction with 100 mℓ of chloroform. The chloroform layer was washed with 50 mℓ of 2N hydrochloric acid and then concentrated to give 0.60 g of 1-acetyl-1,2-dimethyl-3-nitroisothiourea as pale yellow liquid. NMR ($CDCl_3$):2.23(3H, s), 2.52(3H, s), 3.17(3H, s).

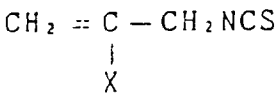
To a mixture of 0.514 g of 1-acetyl-1,2-dimethyl-3-nitroisothiourea and 5 mℓ of toluene was dropwise added a mixture of 0.400 g of 5-(aminomethyl)-2-chlorothiazole, 10 mℓ of toluene and 2 mℓ of ether under cooling with ice over 10 min. The mixture was stirred under cooling with ice for 2 hours, and white crystals formed were collected by filtration to give 0.230 g of N-acetyl-N'-(2-chloro-5-thiazolymethyl)-N-methyl-N''-nitroguanidine (reference compound No.7), mp 105 - 108° C. NMR ($CDCl_3$):2.11(3H, s), 3.08(3H, s), 4.57(2H,

4. A process for preparing 5-(aminomethyl)-2-chlorothiazole



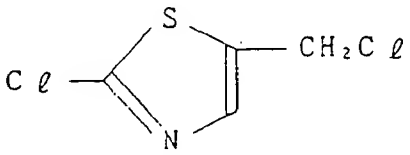
(Ⅲ)

or salts thereof which comprises reacting an allyl isothiocyanate derivative represented by the formula



(Ⅱ)

wherein X represents a leaving group with a chlorinating agent to produce 2-chloro-5-(chloromethyl)-thiazole represented by



(Ⅰ)

and then reacting the resulting compound with an aminating agent.

5. A process according to Claim 4 wherein X in the formula [Ⅱ] is a chlorine atom.

6. A process according to Claim 4 wherein the chlorinating agent is chlorine or sulfuryl chloride.

7. A process according to Claim 4, wherein the aminating agent is ammonia.

8. A process according to Claim 4, wherein the aminating agent is potassium phthalimide or sodium phthalimide.

9. A process according to Claim 4, wherein the aminating agent is hexamethylenetetramine.

10. A process according to Claim 4, wherein the aminating agent is liquid ammonia.

11. A process for preparing 5-(aminomethyl)-2-chlorothiazole or salts thereof which comprises reacting 2-chloro-5-(chloromethyl)thiazole with liquid ammonia.

12. A process for preparing 5-(aminomethyl)-2-chlorothiazole or salts thereof which comprises reacting 2-chloro-5-(chloromethyl)thiazole with hexamethylenetetramine.